Testosterone replacement and improved memory

Corey Lyon DO Alicia Wong MD MPH MA Kristen DeSanto MSLS MS RD AHIP

Clinical Inquires question

Does testosterone replacement improve cognition in memory-impaired older men with low testosterone?

Evidence-based answer

Testosterone therapy does not appear to improve cognition in older men with low testosterone and memory impairment (strength of recommendation B, based on systematic reviews of small, low-quality randomized controlled trials [RCTs] and individual, small RCTs).

Evidence summary

A subgroup analysis of a review that included a coordinated set of 7 double-blind placebo-controlled trials that initially assessed efficacy of testosterone for sexual and physical function in older men evaluated the daily use of 1% testosterone gel (5 g daily) at both 6- and 12-month intervals among men 65 years and older with age-associated memory impairment.[1] The subgroup included 493 men (n=247 receiving testosterone and n=246 receiving placebo) with a mean serum testosterone concentration less than 9.20 nmol/L and age-associated memory impairment, defined as having both subjective memory complaints (score of 4 or 5 on at least 1 item of the Memory Assessment Clinics questionnaire) and performance on delayed paragraph recall and visual memory 1 SD below performance of men aged 20 to 24 years but not greater than 2 SD below age-matched men. Exclusion criteria were severe depression (Patient Health Questionnaire–9 score ≥20) and cognitive impairment (Mini-Mental State Examination [MMSE] score <24). Testosterone dose was adjusted to reach a goal of 17 to 28 nmol/L. No significant differences were found between the testosterone and placebo groups in their measures of delayed paragraph recall (Wechsler Memory Scale-Revised Logical Memory I), visual memory (Benton Visual Retention Test), executive function (Trail Making Test A and B), or spatial ability (Card Rotation Test).

An RCT of 22 patients with mild cognitive impairment and low to low-normal testosterone (<10.4 nmol/L) evaluated the effectiveness of testosterone replacement on cognition.[2] Mean age of the patients was 70.5 years, and they were diagnosed with mild cognitive impairment by various tests that measure visual, spatial, and verbal memory, and language fluency and attention. Randomized patients applied either placebo or testosterone gel (50 to 100 mg daily) titrated to a goal testosterone level of 17 to 31 nmol/L, which was tested on day 7 and 14 and at 1 and 3 months. At 6 months, there was no difference between groups in any testing of attention, spatial abilities, visual memory, verbal memory, language fluency, or working-memory tasks.

An RCT of 11 patients older than 65 years with low testosterone and mild to moderate cognitive impairment examined the effectiveness of testosterone on cognition over 3 months.[3] Patients' serum testosterone levels were below 4.5 nmol/L, and MMSE scores were between 14 and 28. Patients (age range 73 to 87) were randomized to receive 200 mg of intramuscular testosterone every 3 weeks or a matching placebo injection. At 10 weeks, there was no difference from baseline between the groups in MMSE score (testosterone group, -25.5 to -26; placebo group, -21.8 to -22.6; no *P* value provided) or in the Dementia Rating Scale (0 to 144, with higher scores equaling lower cognition; testosterone group, 118 to 122; placebo group, 109 to 110).

An RCT of 10 patients with Alzheimer's disease and low testosterone evaluated the effectiveness of testosterone replacement on cognition.[4] Patients had a testosterone level less than 8.7 nmol/L and mean age was 68.9 years in the placebo group and 72.4 in the testosterone group. Patients were randomized to receive 200 mg intramuscular testosterone every 2 weeks or matching placebo. The testosterone group had a mean Alzheimer's Disease Assessment Scale cognitive subscale (0 to 70; higher scores equal lower cognition) score of 25 and experienced an improvement of 7.2 at 3 months and 9.6 at 9 months (*P*=.02), but only 4.8 at 12 months compared with baseline (*P* value only provided for 9 months). The placebo group improved by 4 points at 3 months, but worsened by 7 points at 9 months (no data for 12 months provided and no *P* values provided).

Dr Lyon is Associate Professor of Family Medicine, **Dr Wong** is an instructor and fellow in family medicine, and **Ms DeSanto** is a clinical librarian, all at the University of Colorado in Denver.

References

1. Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA* 2017;317(7):717-27.
2. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. *Am J Alzheimers Dis Other Demen* 2014;30(4):421-30.
3. Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci* 2004;59(1):75-8.
4. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male* 2003;6(1):13-7.

Can Fam Physician 2021;67:e9. DOI: 10.46747/cfp.6701e9